Consistent with the Examiner's request (page 2 of the Office Action), Applicants have enclosed (in Appendix C) a copy of all pending claims.

II. THE ASSERTION OF LACK OF UNITY OF INVENTION IS TRAVERSED BECAUSE CLAIMS 18 AND 19 ARE PATENTABLE OVER JOHANSEN AND DICKELY

Applicants acknowledge, with appreciation, the indication in the Office Action that Richardson et al. (*J Dairy Sci* 66:2278-2286) does not teach or suggest the methods of Group I, as set forth in claims 1-3, 8-11 and 26. Office Action, page 2.

With respect to claims 18 and 19 of Group II, it was stated in the Office Action that the modified lactic acid bacterium of these claims were known in the prior art. Johansen et al. (*Dev Biol Stand* 85:531-34) and Dickely et al. (*Mol Microbiol* 15:839-847) were cited as examples of prior art which, allegedly, made such bacterium known. Office Action, page 2. In particular, it was stated that Johansen and Dickely disclosed purine auxotrophic strains, e.g., DN209, of *Lactococcus lactis* as allegedly claimed by claims 18 and 19. It was acknowledged that these two references do not teach resistance of such auxotrophic strains to lysis by bacteriophage, but it was asserted that the strains would allegedly inherently exhibit this characteristic as being purine auxotrophs. Office Action, page 2. It was concluded that the bacteria of Group II do not constitute a special technical feature as defined by PCT Rule 13.2. Claims 18-23 (Group II) were withdrawn from further consideration as being directed to a non-elected invention. *Id.*

Applicants respectfully traverse this assertion. Applicants respectfully point out that Johansen discloses the mutation of the purine-auxotroph strain DN209 which, in its mutated state, is capable of growing in the absence of purine in a medium, e.g., *see* Johansen, page 533.

Dickely describes the development of food-grade cloning vectors and a system of nonsense suppressors and nonsense mutants. The system may be used for genetic analysis of *Lactococcus* and their plasmids and bacteriophages (*see* Dickely, page 844).

None of these two articles discloses or suggests that auxotrophic lactic acid bacterial strains retain their metabolic activity when they are cultured in a medium lacking the compound for which the bacterium strains are auxotrophe. For at least these reasons, Applicants respectfully submit that claims 18-23 share the same special technical feature as claims of Group I.

Applicants request that claims of Groups I and II be examined in the application.

III. OBJECTIONS TO SPECIFICATION.

In the Office Action it was suggested that the title of the invention was not descriptive and a new title was required to clearly indicate the invention to which the claims were directed. The suggested title was "Method of Preventing Bacteriophage Infection Using Auxotrophic Lactic Acid Bacteria". MPEP, § 606.01 was cited in support of this assertion. Office Action, page 3.

Applicants respectfully submit that the title of the invention need not be amended, at least once the Examiner considers Applicants' claim amendments and their arguments included in this Amendment.

The specification was also objected to because there was no brief description of the drawings section. Office Action, page. Applicants have now amended the specification to provide a title of such section to the existing description of drawings.

It was also indicated that the sequence listing had been entered into the database with modification, i.e., non-ASCII "garbage" had been deleted at the end of the file.

It was also asserted that Applicants had not complied with at least one condition for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(c), i.e., that an application in which the benefit of an earlier application is desired must contain a specific reference to the prior application in the first sentence of the specification. (37 C.F.R. § 1.78).

Applicants have inserted such a first sentence into the specification.

IV. OBJECTIONS TO CLAIMS.

Claims 24 and 25 were objected to as being dependent upon non-elected claims. Office Action, page 3.

Applicants submit that this objection is moot since claims 24 and 25, in fact, satisfy the unity of invention rules, and claim 21 (from which claims 24 and 25 depend), along with claims 24 and 25, should be considered on the merits in the application.

Claim 27 was also objected to because of a grammatical informality. Applicants amended claim 27 consistent with the Examiner's kind suggestion. The amendment of claim 27 is not related to patentability or substance of the claim, but merely corrects a minor error.

V. AMENDED CLAIM 26 OVERCOMES REJECTION THEREOF UNDER 35 U.S.C. § 101

Claim 26 was rejected under 35 U.S.C. § 101 because, allegedly, the claimed recitation of a use without including any steps involved in the process results in an

improper definition of a process. Office Action, pages 3-4. Applicants' amendment of claim 26 overcomes this alleged rejection.

VI. CLAIMS IN THE APPLICATION PRIOR TO THE AMENDMENT HEREIN MET THE REQUIREMENTS OF 35 U.S.C. § 112, SECOND PARAGRAPH. THE AMENDED CLAIMS CONTINUE TO MEET THOSE REQUIREMENTS

Claims 1-17, 26 and 27 were rejected as allegedly being indefinite for failing to satisfy the requirements of 35 U.S.C. § 112, second paragraph, based on several different reasons. Applicants traverse the assertion that the claims (prior to their amendment herein) were indefinite. Nonetheless, in the interest of expediting prosecution, they have amended most of the aforementioned claims, substantially in the manner suggested by the Examiner.

Applicants note that on page 4, section 21 of the Office Action, claim 1 and the claims which depend therefrom were rejected for the use of "attack by bacteriophages." The USPTO stated that "no definition has been provided." Applicants respectfully direct the Examiner's attention to page 6, lines 10-16 where "not susceptible to attack by bacteriophages" is clearly defined. For at least this reason, the rejection is respectfully traversed.

The amended claims continue to be definite under 35 U.S.C. § 112, second paragraph.

VII. APPLICANTS' CLAIMS, PRIOR TO THEIR AMENDMENT HEREIN, SATISFIED THE REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH. THE AMENDED CLAIMS CONTINUE TO SATISFY THAT REQUIREMENT.

A. Applicants' Original Claims Satisfied The Written Description Requirement and The Amended Claims Continue To Do So.

Claims 1-17 and 24-27 were rejected under 35 U.S.C. § 112, first paragraph, because, allegedly, they contained subject matter which "was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Office Action, page 5. For instance, it was stated that "[t]he specification teaches only a single representative species of such substrates as encompassed by the claims, i.e. milk, two representative species of such bacteria as encompassed by the claims, i.e., purine or thymidine auxotrophic lactic acid bacterium, a single representative species of genetic modifications as encompassed by the claims, i.e., overexpression of F1-ATPase. Moreover, the specification fails to describe any other representative species of substrates, bacteria, or modifications by any identifying characteristics or properties other than being a substrate material, a food or feed product..."(See paragraph bridging pages 5-6, et seq.).

Applicants respectfully traverse this rejection. It appears that an attempt was made in the Office Action to impermissibly limit the claimed invention only to the examples provided. It appears that Applicants are required to limit their claims only to auxotrophic lactic acid bacteria, one particular substrate, i.e., milk, and one particular embodiment of genetic modification. This is improper because the specification contains a written description (and enablement) for a broader scope of the claimed invention. For example, the specification includes a number of bacterial strains which can be used in the invention, e.g., page 18, lines 21-28, a number of substrates, e.g., page 10, lines 29-page 11, line 3 and a number of mechanisms, which can be used to provide a suitable bacteria or bacterial cultures, e.g., page 8, line 7-page 9, line 25.

The written description requirement is satisfied if Applicants' specification indicates that as of its filing date, Applicants had possession of the subject matter claimed. As recently stated by the Board of Patent Appeals and Interferences, to meet

that requirement, an applicant does not have to utilize any particular form of disclosure to describe the claimed subject matter, but "the description must clearly allow persons of ordinary skill in the art to recognize that the applicant invented what is later claimed. Put another way, the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Argyropoulos v. Swarup*, 56 USPQ 2d 1795, 1806 (unpublished) (BPAI 2000) citing *In re Gosteli*, 10 USPQ2d 1614 (Fed. Cir. 1989) and *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991).

As discussed in detail above, Applicants' specification, including the disclosure of a number of specific species provides a clear indication that Applicants, at the time their application was filed, possessed the subject matter of their entire claimed invention. In this connection, Applicants respectfully traverse the assertion in the Office Action that their specification teaches only a single representative species of the substrate, i.e., milk, only two representative species of the bacteria and a single representative species of a genetic modification. As discussed above, the specification provides numerous examples of the substrates, bacterial strains and genetic modifications which can be used. As stated by the Board in *Argyropoulos*, *supra*, Applicants' specification can meet the written description requirement without utilizing any particular form of the disclosure. In the instant case, Applicants have chosen to satisfy that requirement by describing the invention generically, including a description of a number of specific species in their specification, and a description of a number of specific examples. In summary, Applicants have established that, when they filed their application, they had possession of the full scope of their claims.

B. Applicants' Original and Amended Claims Meet the Enablement Requirement.

Claims 1-17, and 24-27 were also rejected under 35 U.S.C. § 112, first paragraph, as non-enabling for the genus of the claim. Office Action, pages 6-7. For instance, it was stated that the claimed invention relates to a method for modifying any substrate or manufacturing any food or feed product using all modified lactic acid bacterium through the use of: lactic acid bacteria with any mutation that renders the strain auxotrophic and thus disrupts DNA, RNA or protein synthesis while the modified strain is capable of carrying out any metabolic reaction and is not susceptible to bacteriophage attack. Office Action, pages 6-7. It was concluded that the specification fails to enable a person skilled in the art to make and/or use the invention commensurate with the scope of the claims. Office Action, page 7.

As with the written description rejection, the enablement rejection appears to be an attempt to force Applicants to impermissibly limit their claimed invention only to the specifically exemplified embodiments. Applicants respectfully traverse this rejection.

It is well established that specification of a patent application satisfies the enablement requirement if the scope of claims in question is enabled so that persons of ordinary skill in the art would be able to make the claimed invention without undue experimentation. The question of undue experimentation is a matter of degree. If some experimentation is necessary, it does not preclude enablement, so long as such experimentation is not unduly extensive, *PPG Industries, Inc. v. Guardian Industries Corp.*, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996). In the *PPG Industries* case, the court also held that

> "[W]here the specification provides 'guidance in selecting the operating parameters that would yield the claimed result, it is

> fair to conclude that the experimentation required to make a particular embodiment is not 'undue.'"

PPG Industries, Id. at 1624.

Similarly, in another case (*Johns Hopkins University v. Cellpro Inc.*, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998)), the Federal Circuit found enablement in a patent specification disclosing only one method of producing one antibody for a claim directed to a broader genus of antibodies. The court made that finding based, *inter alia*, on a Declaration submitted by an opposing party's (a defendant in a patent infringement litigation) expert that the disclosure of the specification of the patent was sufficient for him to make antibodies other than that disclosed in the specification. The expert stated in the Declaration that he had to use some experimentation to obtain that result. The court concluded that such routine experimentation does not constitute undue experimentation. *Johns Hopkins, id* at 1718-19.

As pointed out in the Office Action, the Federal Circuit set forth the following factors to be considered in determining if undue experimentation is required:

(1) the quantity of experimentation necessary;

(2) the amount of direction or guidance presented;

(3) the presence or absence of working examples;

(4) the nature of the invention;

(5) the state of the prior art;

(6) the relative skill of those in the art;

(7) the predictability or unpredictability of the art; and

(8) the breadth of the claim(s).

In re Wands (858 F.2d 731, 8 USPQ 2d 1400, Fed Cir 1988).

Applicants have provided a teaching which enables those skilled in the art to practice the claimed invention. For example, Applicants have disclosed a number of parameters for practicing their invention. Applicants provided the disclosure of the

properties of certain bacterial cultures, such as that of lactic acid bacterium, having an acidification rate in milk of at least 1% to at least 25% of the culture which, when it is present in a substrate material, is capable of DNA replication, RNA transcription and/or protein synthesis. *See* page 10, lines 4-14. Applicants also provided a disclosure of concentration of the bacterial strain, e.g., 10^5 to 10^9 CFU/ml or g of the material. *See* page 10, lines 16-21. Applicants additionally disclosed different types of non-proliferating cells which can be used, such as "resting cells" or "non-dividing cells". *See*, e.g., page 12, lines 11-17. Examples provide additional detailed disclosure of some specific embodiments of the invention which further enhance the enabling nature of Applicants' general disclosure.

For at least the above reasons, the specification meets the enablement requirement.

C. Dr. Nillson's Declaration Provides Further Proof That The Specification Satisfies The Written Description and Enablement Requirements.

In addition to meeting the written description and enablement requirements in the specification as filed, Applicants submit herewith a Declaration of Dan Nilsson, Ph.D. Dr. Nilsson described a study he conducted to demonstrate that the invention disclosed and claimed in the application can be easily used by persons of ordinary skill in the art with substrates other than milk. Dr. Nilsson's studies were conducted with *Lactococcus lactis* MBP71 (*thyA*) from Example 2 of the application and milk and the following additional substrates: M17 medium and M17 + 0.5% of lactose, SA medium as well as SA + 1% of lactose ("LSA medium"). Furthermore, the culture used was either MBP 71 or MBP and thymidine. *See* section 5 of Dr. Nilsson's Declaration.

Dr. Nilsson concluded that, based on the examples and the specification, he "....could make use of the entire scope of the present invention." See last paragraph of section 5, page 3. It is clear from Dr. Nillson's Declaration that he did not have to engage in undue amount of experimentation to practice various aspects of the invention.

D. Claims 4 and 5 Satisfy 35 U.S.C. § 112, First Paragraph

Claims 4 and 5 were rejected under 35 U.S.C. § 112, first paragraph, because the bacteria recited in those claims should have been deposited according to 37 C.F.R. §§ 1.801-1.809. Applicants wish to advise that the bacteria were deposited under the terms of the Budapest Treaty. Applicants will provide an affidavit or a declaration stating that the strains have been deposited under the Budapest Treaty and including other representations required by the rules.

VIII. APPLICANTS' CLAIMS ARE NON-OBVIOUS OVER THE CITED REFERENCES

35 U.S.C. §103(a)

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Initially, Applicants point out that the present invention may generally be described as a method of modifying a substrate material by means of a bacterial culture which is capable of being metabolically active in said substrate, whereby the bacterial culture is not susceptible to attack by bacteriophages, the method comprising (i) isolating a bacterial strain which is not capable of DNA replication, RNA transcription or protein synthesis in said substrate material but is capable of metabolically modifying the

substrate material, (ii) propagating the isolated bacterial strain in a medium wherein the strain is capable of replicating to obtain a bacterial culture of said strain, (iii) adding the thus obtained bacterial culture to the substrate material and keeping the substrate material under conditions where the culture is metabolically active, and whereby, if the substrate material is contaminated with a bacteriophage, the metabolic activity of the bacterial culture is substantially unaffected by the bacteriophage.

A. Rejection Over Dickely, Daly and Doskocil.

On pages 10-13, section 15 of the Office Action, the USPTO rejected claims 1-4, 6-10, 15-17 and 24-27 as purportedly unpatentable over Dickely (U.S. Patent 5,691,185) in view of Daly (Antonie van Leeuwenhoek 70:90-110, 1996) and Doskocil (Biochem et Biophys Acta 145:780-791, 1967). The USPTO said that Dickely teaches "purine auxotrophic mutants (Pur-) of L. lactis that require sufficient amounts of purine nucleotides for replication (column 11) and methods of isolating such mutants (column 25). It was stated that Daly teaches "lactic acid bacteria, including genus Lactococcus, is essential for the fermentation of a variety of food products such as milk." Office Action, page 11. Finally, the USPTO stated that Doskocil teaches "5-azacytidine, a cytidine analog, strongly inhibits the production of viable phage particles (page 780, summary) and teaches the mechanism of inhibition of phage production by 5-azacytidine is the inhibition of DNA synthesis (page 789), while protein and RNA synthesis remain largely unaffected (pages 780 and 790)." *Id.*

It was also stated that

> "one of ordinary skill in the art would have recognized that methods of fermenting milk using L. lactis are well known in the art, that Pur⁻ mutants of L. lactis are unable to undergo

> mitosis in a medium lacking purine nucleotides because of the inability to synthesize DNA due to the disruption of purine metabolism, and Pur⁻mutants of L. lactis that remain metabolically active necessarily increase in size."

Office Action, pages 11-12.

It was concluded that one of ordinary skill in the art would have found it obvious

> to combine the teachings of Daly, Doskocil, and Dickely to use the Pur⁻mutants of Dickely for growth of a starter culture of the Pur⁻mutants in a growth medium supplemented with purines, removal of the starter culture cells from the growth medium, and fermentation of milk using the L. lactis Pur⁻ mutants and optionally to include 5-azacytidine in order to prevent bacterial lysis by phage. One would have been motivated to ferment milk using the Pur⁻ L. lactis of Dickely and optionally including 5-azacytidine because L. lactis Pur⁻ mutants would be unable to synthesize DNA as milk provides insufficient purines to support growth of the L. lactis Pur⁻mutants, thereby preventing lysis by phage. One would have a reasonable expectation of success for using the Pur⁻ mutants of Dickely for growth of the Pur⁻mutants in a growth medium supplemented with purine nucleotides, removal of the cells from the growth medium, and fermentation of milk using the Pur⁻ L. lactis mutants and optionally to include 5-azacytidine in order to prevent bacterial lysis by phage because of the results of Daly, Doskocil, and Dickely.

Office Action, page 12.

Applicants respectfully disagree and traverse this rejection.

As stated by the Federal Circuit, "a proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In addition, the prior art reference(s) must teach or suggest all of the claim

limitations. The teaching or suggestion to combine and the reasonable expectation of success must both be found in the prior art, and not in Applicant's disclosure. *Id* at 493. *See also* M.P.E.P. § 2142.

Initially, Applicants thank the Examiner for noting that "Dickely does not teach the use of Pur-mutant L. lactis for fermentation of a substrate material, a substrate material containing a compound that inhibits DNA replication, RNA transcription, or protein synthesis, or a food or feed product." Office Action, page 11. Applicants note that Dickely is directed to a nonsense suppressor capable of replicating in a lactic acid bacterium, particularly as a means for maintaining the desired gene. The claimed invention is not directed solely to an auxotrophic bacteria or to L. lactis which can ferment a substrate material. Rather the claimed invention is directed to the surprising results and methods of modifying substrates with a bacterium which is "not susceptible to attack by bacteriophages" but remains metabolically active.

Further, Applicants note that Daly describes biotechnological uses of lactic acid bacterial culture with a focus on different phage-resistance and states that such infections are a major problem in the art. Daly does not suggest new methods for dealing with the problem of phage infection but rather describes the need for new methods. The claimed invention is such a new and non-obvious method for dealing with the problems discussed in Daly.

Doskocil describes how 5-azacytidine affects lactic acid bacterial cultures, primarily by inhibiting the growth of the bacteriophage. Doskocil describes a compound which inhibits certain bacteriophages. This is different from the claimed invention in several respects. Initially, Doskocil does not appear to discuss if the bacterial strain remain metabolically active following the addition of the inhibitor. Further, the Applicants

note that Doskocil is directed toward the addition of an inhibitor following bacteriophage infection.

The Examiner has provided no reasons why one of ordinary skill in the art would be motivated to combine the above references. Certainly, one would not be motivated to combine a general teaching of bacteriophage infection (Daly) with a bacteriophage inhibitor and/or a nonsense suppressor and achieve the claimed invention.

Applicants also point out that the fact that a claimed product (or method) is within a broad field of the prior art and one might arrive at it by selecting specific items and conditions does not render the product obvious in the absence of some directions or reasons in the prior art for making such selections. *Ex parte Kuhn*, 132 U.S.P.Q. 359 (Pat. & Tr. Office Bd. App.)(1961). Similarly, in *In re Baird* the court recognized that a compound within the scope of a generic formula which encompasses more than 100 million compounds does not make obvious the motivation for the selection of specific compounds. (29 U.S.P.Q.2d 1550, (1994)). Indeed, in *In re Baird*, dissimilarly to the present situation the claimed invention was actually encompassed by the general formula of the prior art.

Prior art references in combination do not make an invention obvious unless something in the prior references would suggest the advantage to be derived from combining their teachings. *In re Semaker*, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). In the present case, the USPTO has done no more than find some of the separate elements of the present invention and argue that broad disclosures which would require specific selection and experimentation to achieve the current invention, render the present invention obvious.

A combination may be patentable whether it is composed of elements all new, partly new or all old. *Rosemont, Inc. v. Beckman Instruments, Inc.*, 221 U.S.P.Q. 1, 7 (Fed. Cir. 1984). There must be something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *Lindemann v. Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). *Interconnect Planning Corporation v. Feil, et al.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). In the present case there is no such motivation. It is improper to pick and choose among individual parts of assorted references as a mosaic in an effort to recreate a facsimile of the claimed invention. *AKZO N.V. v. International Trade Commission*, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986). *Uniroyal v. Rudkin-Wiley*, 5 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988). In the present case the Applicants have shown that their invention is not within the general teachings of the prior art. Thus, there would be no motivation provided by prior art to obtain the claimed method of modifying a substrate material by means of a bacterial culture which is capable of being metabolically active in said substrate (even in the absence of a nutrient needed for its growth), whereby the bacterial culture is not susceptible to attack by bacteriophages. Such a method if simply not suggested by the prior art.

If motivation were to exist, which it does not, one would not be motivated to use the methods of Dickely, Daly, Doskocil and/or Ross, to provide the claimed bacterial strain which is capable of providing metabolic activity while not being susceptible to attack by bacteriophages. Indeed, the statutory standard of 35 U.S.C. §103 is whether the invention, considered as a whole, would have been obvious to one of ordinary skill in the art, not whether it would have been obvious for one of ordinary skill in the art to try various combinations. *Akzo N.V. v. E.I. duPont de Nemours*, 1 U.S.P.Q.2d 1705,

1707 (Fed. Cir. 1987). Where the prior art discloses no particular preference for the component claimed from among a number of other components disclosed in a reference, i.e., where there is no disclosure within the prior art that would have led the routineer to make the critical selections to arrive at the claimed composition, the court found a rejection for obviousness could not be sustained. *Ex parte Wittpenn*, 16 U.S.P.Q.2d 1730, 1731 (PBAI 1990).

For all the above reasons, the rejection is respectfully traversed.

B. Rejection of Claim 5 Over Dickely in View of Daly and Doskocil and Ross

On pages 13-14, section 16 claim 5 was rejected over the above references further in view of Ross (Appl Envirn Microbiol 56:2164-2169, 1990). In particular, it was stated that Ross teaches that thymidylate synthase (TS) plays a key role in DNA synthesis and that cells with the mutation "require thymine or thymidine for DNA synthesis and growth and die in the absence of thymine or thymidine." (Office Action page 13). The abstract of Ross and the Examiner noted that Ross's "thyA mutants cannot survive in environments containing low amounts of thymidine or thymine unless complemented by the thyA gene." *See* Ross, Abstract. If the thyA gene is present, then the bacterial strain grows in a normal fashion. Neither the USPTO nor the Ross reference have provided any reason to believe that the mutants of Ross would not be susceptible to attack by bacteriophages. The mutants of Ross were designed as an alternative to antibiotic resistance genes as a functional selection marker. Alternatively, if the mutants are dead in the absence of thymidine or thymine or the thyA gene, they would remain metabolically active. In contrast, in Applicants' invention, the bacterial strain is metabolically active in the absence of a nutrient required for its growth.

Again, the USPTO makes the assumption that it would be obvious to take the mutant of Ross and combine it with the teachings of Dickely, Daly, and Doskocil. It is clear that this is not the case because there is no suggestion or motivation to do so in the prior art. The USPTO is using impermissible hindsight to construct the Applicants' claimed invention. Further as claim 1 is novel and non-obvious, so are claims that depend therefrom, such as claim 5.

For at least the above reasons, the rejection is respectfully traversed.

C. Rejection of Claims 12-14 Over Dickely, Daly, Doskocil and Snoep

On pages 14-15, section 17, claims 12-14 were rejected in view of Dickely, Daly, Doskocil and Snoep (WO 98/10089, 1998). The USPTO stated that Snoep teaches that the overexpression of bacterial F1-ATPase subunit of H^+-ATPase increases carbon flow through the glyclytic pathway by increasing the pool of available ADP, thereby increasing the production of lactic acid, which is important for bacteria involved in acidification and flavoring of dairy products." (Office Action, page 14). Snoep discloses a method for improving the production of biomass or a desired product from a cell by adjusting the ratio of ATP/ADP in the cell. Again, the USPTO apparently made the assumption that it would be obvious to take the teachings of Snoep and combine it with the teachings of Dickely, Daly, and Doskocil. The USPTO stated that "one would have been motivated to ferment milk using the Pur-L. lactis of Dickely overexpressing the F1-ATPase of Snoep in order to increase the production of lactic acid for a more rapid fermentation of milk." Office Action, page 14. The USPTO has not provided evidence as to why it would have been obvious to one of ordinary skill in the art to combine the cited references. The references themselves do not suggest their combination. The USPTO is using impermissible hindsight to construct the Applicants' invention. Further

it is respectfully pointed out that claim 1 is novel and non-obvious for the reasons detailed above. Thus, claims 14-15 that depend from claim 1 are also novel and unobvious.

For all the above reasons, the rejection is respectfully traversed.

D. Rejection of Claims 11 Over Dickely, Daly, Doskocil and Barach

On pages 15-16, section 18, claim 11 was rejected over Dickely, Daly, Doskocil and further in view of Barach (U.S. 4,294,930). The USPTO states that Barach teaches to "facilitate handling and uniformity of a starter culture for milk fermentation, an effective microbial cell population is usually greater than about 10^8 CFU/ml." Office Action, page 15.

Initially, Applicants assert that for the above stated reasons the claim is novel and non-obvious as it depends from a novel and non-obvious claim 1. Furthermore, Barach does not add anything to the teachings of Dickely, Daly and Doskocil to render the combination of claims 1 and 11 obvious. For example, Barach fails to suggest, much less disclose, a method of modifying a substrate material with a bacterial culture which is metabolically active in the substrate, which is not susceptible to attack by bacteriophages, such that in the presence of the bacteriophages in the substrate material the bacterial culture substantially retains its metabolic activity, with the bacterial strain at any concentration, much less at the concentration specifically recited in claim 11. (Of course, claim 11 also requires that the bacterial strain is not capable of DNA replication, RNA transcription or protein synthesis in the substrate material, but is capable of metabolically modifying the substrate material. These features are not suggested by Barach or the other three references.)

The rejection is respectfully traversed.

CONCLUSION

Applicants respectfully submit that the application is in condition for allowance and request a notice of allowance for all the pending claims. Should the Examiner determine that any further action is necessary to place this application in condition for allowance, the Examiner is kindly requested and encouraged to telephone Applicants' undersigned representative at the number listed below.

It is believed that no fees (other than those authorized herein) are due in connection with this response. However, if any additional fees are determined to be due, the Commissioner is hereby authorized to charge such fees to the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,

HUNTON & WILLIAMS

Dated: August 27, 2002

By: _____

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APPENDIX A

On page 1, after line and before line 3, please insert the following paragraph:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national phase of PCT Application, PCT/DK99/00382, filed July 2, 1999 which was published in English on January 13, 2000. This application claims priority from Denmark patent application PA 1998 00878 of July 3, 1998 and U.S. Provisional Patent application 60/091,735 of July 6, 1998. The contents of all the above-identified patent applications are incorporated herein by reference to the extent they are consistent with this application and the inventions described herein.

On page 14, after line 20 and before line 21, please add the following heading.

BRIEF DESCRIPTION OF THE DRAWINGS

APPENDIX B

1. (Once amended) A method of modifying a substrate material by means of a said bacterial starter culture [which is] being capable of being metabolically active in said [substrate] food and/or feed product starting material, [whereby] the bacterial culture not being susceptible to attack by bacteriophages, bacterial starter culture made by a [the] method comprising

(i) isolating a bacterial strain which is not capable of DNA replication, RNA transcription or protein synthesis in said [substrate] food and/or feed product starting material but is capable of metabolically modifying the [substrate] food and/or feed product starting material,

(ii) propagating the [selected] isolated bacterial strain in a medium wherein the strain is capable of replicating to obtain [a] the bacterial starter culture of said strain.

[(iii) adding the thus obtained bacterial culture to the substrate material and keeping the material under conditions where the culture is metabolically active.

whereby, if the substrate material is contaminated with a bacteriophage, the metabolic activity of the bacterial culture is substantially unaffected by the bacteriophage.]

4. (Once amended) A method according to claim 3 wherein the mutant strain is a Pur$^-$ mutant [including *Lactococcus lactis* strain DN105 deposited under the accession number DSN 12289].

5. (Once amended) A method according to claim 3 wherein the mutant strain is a *thyA* mutant [including *Lactococcus lactis* strain MBP71 deposited under the accession number DSM12891].

7. (Once amended) A method according to claim 1 wherein the substrate material [contains] comprises at least one compound that inhibits the DNA replication, RNA transcription or the protein synthesis of the bacterial strain.

8. (Once amended) A method according to claim 1 wherein the substrate material is a starting material for an edible product, [the material is selected from the group consisting of] comprising milk, a vegetable material, a meat product, a must, a fruit juice, a wine, a dough [and] or a batter.

10. (Once amended) A method according to claim 9 wherein the bacterial culture is a culture of *Lactococcus lactis*.

11. (Once amended) A method according to claim 1 wherein the bacterial [strain is] culture added to the substrate material includes the bacterial strain at a concentration in the range of 10^5 to 10^9 CFU/ml or g of the material.

12. (Once amended) A method according to claim 1 where the bacterial culture comprises a genetically modified strain which, relative to its parent strain is enhanced in at least one metabolic pathway.

17. (Once amended) A method according to claim 1 wherein the bacterial culture comprises a bacterial strain which is capable of increasing the size of the cells without mitosis.

18. (Once amended) A modified lactic acid bacterium that is modified to become incapable of performing DNA replication, RNA transcription or protein synthesis in a specifically defined substrate material which is limited with respect to at least one compound that is required by the bacterial strain for DNA replication, RNA transcription or protein synthesis, said modified bacterial strain is capable of being metabolically active in said substrate material, whereby the strain is not susceptible to attack by bacteriophages, subject to the limitation, that the lactic acid bacterium is not a strain selected from the group consisting of strain DN101, DN102, DN103, DN104 and DN105 (DSM12289).

23. (Once amended) A composition according to claim 22 which further [comprising] comprises at least [on] one component enhancing the viability of the bacterial [active ingredient] culture during storage including a bacterial nutrient or a cryoprotectant.

26. (Once amended) [Use of] A method of preparing a [culture as obtained in the method of claim 1 as] food and/or a feed product, comprising adding a bacterial starter culture [in the preparation of a product selected from the group consisting of a dairy flavour, a product for cheese flavouring, a food product and a feed product] to a food and/or a feed product starting material, said bacterial starter culture being capable of being metabolically active in said food and/or feed product starting material, the bacterial starter culture not being susceptible to attack by bacteriophages, the bacterial starter culture made by a method comprising

(i) isolating a bacterial strain which is not capable of DNA replication, RNA transcription or protein synthesis in said food and/or feed product starting material but is capable of metabolically modifying the food and/or feed product starting material,

(ii) propagating the isolated bacterial strain in a medium wherein the strain is capable of replicating to obtain the bacterial starter culture of said strain, and

(iii) maintaining the thus-obtained inoculated food and/or feed product starting material under such conditions that the bacterial strain of the bacterial starter culture is metabolically active,

whereby, if the food and/or feed product starting material is contaminated with a bacteriophage, the metabolic activity of the bacterial starter culture is substantially unaffected by the bacteriophage.

27. (Once amended) A method of preventing a lactic acid bacterial starter culture [is infected] infection by bacteriophages in the manufacturing of a food or feed product, the method comprising adding as a starter culture a lactic acid bacterium obtained by the method according to claim 1 to a food or feed product starting material which is limited with respect to at least one compound that is required by the bacterial strain for DNA replication, RNA transcription or protein synthesis and keeping the thus inoculated starting material under conditions where the lactic acid bacterium is metabolically active, whereby, if the substrate material is contaminated with a bacteriophage, the metabolic activity of the bacterial culture is substantially unaffected by the bacteriophage.

28. (New) A method according to claim 4 wherein the mutant strain is *Lactococcus lactis* strain DN105 deposited under the accession number DSM 12289.

29. (New) A method according to claim 5 wherein the mutant strain is *Lactococcus lactis* strain MBP71 deposited under the accession number DSN12891.

30. (New) A method for reducing susceptibility to attack by bacteriophages in a substrate material comprising:

(i) isolating an auxotrophic bacterial strain which maintains its metabolic activity in the absence of the auxotrophic component in the substrate material;

(ii) adding the auxotrophic bacterial strain to said substrate material.

31. (New) A method of preparing a dairy flavouring and/or a product for cheese flavouring comprising, adding a bacterial starter culture to a dairy flavouring and/or a product for cheese flavouring starting material, said bacterial starter culture being capable of being metabolically active in said dairy flavouring and/or product for cheese flavouring starting material, the bacterial starter culture not being susceptible to attack by bacteriophages, the bacterial starter culture made by a method comprising

(i) isolating a bacterial strain which is not capable of DNA replication, RNA transcription or protein synthesis in said dairy flavouring and/or product for cheese flavouring starting material but is capable of metabolically modifying the dairy flavouring and/or product for cheese flavouring starting material,

(ii) propagating the isolated bacterial strain in a medium wherein the strain is capable of replicating to obtain the bacterial starter culture of said strain, and

(iii) maintaining the thus-obtained inoculated dairy flavouring and/or product for cheese flavouring starting material under such conditions that the bacterial strain of the bacterial starter culture is metabolically active,

whereby, if the dairy flavouring and/or product for cheese flavouring starting material is contaminated with a bacteriophage, the metabolic activity of the bacterial starter culture is substantially unaffected by the bacteriophage.

APPENDIX C

1. (Once amended) A method of modifying a substrate material by means of a said bacterial starter culture being capable of being metabolically active in said food and/or feed product starting material, the bacterial culture not being susceptible to attack by bacteriophages, bacterial starter culture made by a method comprising

(i) isolating a bacterial strain which is not capable of DNA replication, RNA transcription or protein synthesis in said food and/or feed product starting material but is capable of metabolically modifying the food and/or feed product starting material,

(ii) propagating the isolated bacterial strain in a medium wherein the strain is capable of replicating to obtain the bacterial starter culture of said strain.

2. A method according to claim 1 wherein the substrate material is limited with respect to at least one compound that is required by the bacterial strain for DNA replication, RNA transcription or protein synthesis.

3. A method according to claim 2 wherein the bacterial strain is a mutant strain being auxothrophic in respect of a compound which is not present in the substrate material and which is required by the strain for replication.

4. (Once amended) A method according to claim 3 wherein the mutant strain is a Pur$^-$ mutant.

5. (Once amended) A method according to claim 3 wherein the mutant strain is a *thyA* mutant.

6. A method according to claim 2 wherein the strain in said substrate material is not capable of performing at least one activity selected from the group consisting of DNA replication, RNA transcription and protein synthesis.

7. (Once amended) A method according to claim 1 wherein the substrate material comprises at least one compound that inhibits the DNA replication, RNA transcription or the protein synthesis of the bacterial strain.

8. (Once amended) A method according to claim 1 wherein the substrate material is a starting material for an edible product, comprising milk, a vegetable material, a meat product, a must, a fruit juice, a wine, a dough or a batter.

9. A method according to claim 1 wherein the bacterial culture is selected from the group consisting of *Lactococcus* spp., *Lactobacillus* spp., *Leuconostoc* spp., *Pediococcus* spp., *Streptococcus* spp., *Propionibacterium* spp., *Bifidobacterium* spp., *Staphylococcus* spp., *Micrococcus* spp., *Bacillus* spp., *Enterobacteriaceae* spp. including *E. coli*, *Actinomycetes* spp., *Corynebacterium* spp. and *Brevibacterium* spp.

10. (Once amended) A method according to claim 9 wherein the bacterial culture is a culture of *Lactococcus lactis*.

11. (Once amended) A method according to claim 1 wherein the bacterial culture added to the substrate material includes the bacterial strain at a concentration in the range of 10^5 to 10^9 CFU/ml or g of the material.

12. (Once amended) A method according to claim 1 where the bacterial culture comprises a genetically modified strain which, relative to its parent strain is enhanced in at least one metabolic pathway.

13. A method according to claim 12 wherein the genetically modified strain has, relative to its parent strain, an enhanced metabolic activity selected from the group consisting of enhanced glycolytic flux and enhanced flux through the pentose phosphate pathway.

14. A method according to claim 13 wherein the genetically modified strain has, relative to its parent strain, an enhanced ATPase activity.

15. A method according to claim 1 wherein the bacterial culture comprises a strain which is a conditional mutant which at a predetermined condition does not perform at least one activity selected from the group consisting of DNA replication, RNA transcription and protein synthesis.

16. A method according to claim 15 wherein the predetermined condition is selected from the group consisting of pH, temperature, composition of the substrate material and presence/absence of an inducer substance.

17. (Once amended) A method according to claim 1 wherein the bacterial culture comprises a bacterial strain which is capable of increasing the size of the cells without mitosis.

18. (Once amended) A modified lactic acid bacterium that is modified to become incapable of performing DNA replication, RNA transcription or protein synthesis in a specifically defined substrate material which is limited with respect to at

least one compound that is required by the bacterial strain for DNA replication, RNA transcription or protein synthesis, said modified bacterial strain is capable of being metabolically active in said substrate material, whereby the strain is not susceptible to attack by bacteriophages, subject to the limitation, that the lactic acid bacterium is not a strain selected from the group consisting of strain DN101, DN102, DN103, DN104 and DN105 (DSM12289).

19. A lactic acid bacterium according to claim 18 wherein the bacterial strain is a mutant strain being auxothrophic in respect of a compound which is not present in the substrate material and which is required by the strain for replication.

20. A lactic acid bacterium according to claim 19 wherein the mutant strain is a *thyA* mutant including *Lactococcus lactis* strain MBP71 deposited under the accession number DSM12891.

21. A starter culture composition comprising the lactic acid bacterium of claim 18.

22. A starter culture composition comprising a lactic acid bacterium obtainable by the method according to claim 1 in combination with at least one further lactic acid bacterium.

23 (Once amended) A composition according to claim 22 which further comprises at least one component enhancing the viability of the bacterial culture during storage

including a bacterial nutrient or a cryoprotectant.

24. A method of manufacturing a food or feed product comprising adding a starter culture composition according to claim 21 to a food or feed product starting material and keeping the thus inoculated starting material under conditions where the lactic acid bacterium is metabolically active.

25. A method according to claim 24 wherein the food product starting material is milk.

26. (Once amended) A method of preparing a food and/or a feed product, comprising adding a bacterial starter culture to a food and/or a feed product starting material, said bacterial starter culture being capable of being metabolically active in said food and/or feed product starting material, the bacterial starter culture not being susceptible to attack by bacteriophages, the bacterial starter culture made by a method comprising

(i) isolating a bacterial strain which is not capable of DNA replication, RNA transcription or protein synthesis in said food and/or feed product starting material but is capable of metabolically modifying the food and/or feed product starting material,

(ii) propagating the isolated bacterial strain in a medium wherein the strain is capable of replicating to obtain the bacterial starter culture of said strain, and

(iii) maintaining the thus-obtained inoculated food and/or feed product starting material under such conditions that the bacterial strain of the bacterial starter culture is metabolically active,

whereby, if the food and/or feed product starting material is contaminated with a bacteriophage, the metabolic activity of the bacterial starter culture is substantially unaffected by the bacteriophage.

27. (Once amended) A method of preventing a lactic acid bacterial starter culture infection by bacteriophages in the manufacturing of a food or feed product, the method comprising adding as a starter culture a lactic acid bacterium obtained by the method according to claim 1 to a food or feed product starting material which is limited with respect to at least one compound that is required by the bacterial strain for DNA replication, RNA transcription or protein synthesis and keeping the thus inoculated starting material under conditions where the lactic acid bacterium is metabolically active, whereby, if the substrate material is contaminated with a bacteriophage, the metabolic activity of the bacterial culture is substantially unaffected by the bacteriophage.

28. (New) A method according to claim 4 wherein the mutant strain is *Lactococcus lactis* strain DN105 deposited under the accession number DSM 12289.

29. (New) A method according to claim 5 wherein the mutant strain is *Lactococcus lactis* strain MBP71 deposited under the accession number DSN12891.

30. (New) A method for reducing susceptibility to attack by bacteriophages in a substrate material comprising:

(i) isolating an auxotrophic bacterial strain which maintains its metabolic activity in the absence of an auxotrophic component in the substrate material;

(ii) adding the auxotrophic bacterial strain to said substrate material.

31. (New) A method of preparing a dairy flavouring and/or a product for cheese flavouring comprising, adding a bacterial starter culture to a dairy flavouring and/or a product for cheese flavouring starting material, said bacterial starter culture being capable of being metabolically active in said dairy flavouring and/or product for cheese flavouring starting material, the bacterial starter culture not being susceptible to attack by bacteriophages, the bacterial starter culture made by a method comprising

(i) isolating a bacterial strain which is not capable of DNA replication, RNA transcription or protein synthesis in said dairy flavouring and/or product for cheese flavouring starting material but is capable of metabolically modifying the dairy flavouring and/or product for cheese flavouring starting material,

(ii) propagating the isolated bacterial strain in a medium wherein the strain is capable of replicating to obtain the bacterial starter culture of said strain, and

(iii) maintaining the thus-obtained inoculated dairy flavouring and/or product for cheese flavouring starting material under such conditions that the bacterial strain of the bacterial starter culture is metabolically active,

whereby, if the dairy flavouring and/or product for cheese flavouring starting material is contaminated with a bacteriophage, the metabolic activity of the bacterial starter culture is substantially unaffected by the bacteriophage.